antigen presenting vesicle is obtained by the step of recovering a 70 000 x g pellet obtained by differential centrifugation of membrane-containing fractions of cell culture media or lysates of B-lymphocytes containing said MHC Class I protein.

17. (New) An antigen presenting vesicle free from its natural surroundings, said vesicle comprising:

a membrane, major histocompatibility complex (MHC) Class I and Class II proteins and one or more at least partially processed antigens bound to said MHC proteins, wherein said antigen presenting vesicle is obtained by the step of recovering a 70,000 x g pellet obtained by differential centrifugation of membrane-containing fractions of cell culture media or lysates of B-lymphocytes containing said MHC Class I and Class II proteins.--.

REMARKS

The Claimed Invention

The claimed invention is directed to an antigen presenting vesicle free from its natural surroundings.

The Pending Claims

Prior to entry of the above amendments, Claims 2-4, 6 and 13 are pending (Claims 9-12 have been withdrawn from consideration). Claims 2-4, 6 and 13 are directed to an antigen presenting vesicle.

The Office Action

Claims 13, 2-4 and 6 stand rejected under 35 U.S.C. 112 first paragraph, and not enabled by the specification.

Claims 13, 2-4 and 6 stand rejected under 35 U.S.C. 112 first paragraph, as not meeting the written description requirement.

Claims 2-4, 6 and 13 stand rejected under 35 U.S.C. 112 second paragraph, as being

indefinite.

Claims 13, 2-4 and 6 stand rejected under 35 U.S.C. 102(b) as being unpatentable over Harding and Gueze (J. Immunol. ISI:3988-3998 (1993) as evidenced by Zitvogel et al (Nature Medicine 4:594-600 (1998).

Claims 13, 2-4 and 6 stand rejected under 35 U.S.C. 102(b) as being unpatentable over Amigorena et al (Nature 369: 113-120 (1994) as evidenced by Zitvogel et al (Nature Medicine 4: 594-600 (1998).

Applicant is required to submit corrected formal drawings.

AMENDMENTS

Claims 2-4 and 6 have been deleted. Claim 13 has been amended and new Claims 14-17 have been added.

Claim 13 is amended to recite (i) the expression "at least partially processed antigens bound to said MHC class I protein" (support for example can be found in the original PCT application claims 3 and 4), and (ii) that the vesicle is obtainable from "a B lymphocyte" (support for example can be found in the original PCT application claim 6).

Basis for new claim 14 can for example be found on page 2, lines 25 to 30 of the PCG patent application and the original PCT claim 9.

Basis for new claim 15 can for example be found in original PCT claims 1, 2, 3 and 6.

Basis for new claim 16 can for example be found in original PCT claims 1, 2, 3, 6 and 9, and on page 2, lines 25 to 30 of the PCT patent application.

Basis for new claim 17 can for example be found in original PCT claims 1, 2, 3, 6 and 9, on page 2, lines 25 to 30 of the PCT patent application and on page 1, lines 3 to 5.

RESPONSE TO THE OBJECTIONS AND REJECTIONS

In response that follows, the Examiner's individual objections and rejections are provided

in full text, as identified by indented small bold print, followed by Applicants response.

35 U.S.C. §112 First Paragraph Rejection, enablement

Claims 13, 2, 3, 4 and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antigen presenting vesicle comprising a membrane and a MHC Class II protein wherein said antigen presenting vesicle is obtainable from an antigen presenting cell, does not reasonably provide enablement for an antigen presenting vesicle comprising a membrane and any MHC Class I protein, or any functional derivative or fragment thereof, wherein said antigen presenting vesicle is obtainable from any cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claims, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claims 3-4, 6 and 13 are drawn to an antigen presenting vesicle comprising a membrane and a MHC Class I protein wherein said antigen presenting vesicle is obtainable from a cell, while claim 2 is drawn to an antigen presenting vesicle comprising a membrane and a MHC Class I or Class II protein wherein said antigen presenting vesicle is obtainable from a cell. The instant specification discloses in its examples, an antigen presenting vesicle derived from B cells only. There is insufficient guidance and direction in the instant specification and the prior art regarding an antigen presenting vesicle from any cell, as evidenced by Janeway et al (Immunobiology 3rd Edition) who teaches that antigens are presented by a limited number of cell types see page 7:15. Janeway also teaches on page 4:11 (Immunobiology 3rd Edition) that the function of MHC Class II molecules is to present peptides generated in the intracellular vesicles of B cells, macrophages and other antigen presenting cells to CD4 T cells. Therefore, it is not routine in the art to isolate antigen presenting vesicles from cells other than antigen presenting cells. Without more guidance and direction form the instant specification, it would required undue experimentation by one of ordinary skill in the art to predict from which cell the recited vesicles can be obtained.

The is insufficient guidance and direction in the instant specification and the prior art regarding the recited antigen presenting vesicles which comprise MHC Class I alone, as evidenced by Zitvogel et al (Nature Medicine 4(5):594-600, May 1998) who teaches that the potential ad advantages of exosomes in immunotherapy is due to its high levels of peptide bound MHC Class I and Class II molecules (see last paragraph of article) and therefore, the existence of the claimed vesicles with only class I and not class II molecules is not evident, and the efficacy of the claimed vesicles with only class I and not class II molecules in immunotherapy as asserted in the instant specification, is not clear. Without more guidance and direction from the instant specification, it would require undue experimentation by one of ordinary skill in the art to make and use the recited vesicles comprising class I and not class II molecules.

There is insufficient guidance and direction in the instant specification and the prior art regarding the isolation of the recited antigen presenting vesicles which comprise a functional derivative or fragment thereof of a MHC Class I protein, as native cells do not routinely produce vesicles with fragment or derivatives of MHC proteins, and because the instant specification neither defines nor describes a functional derivative or fragment thereof of a MHC Class I protein and the prior art does not teach a vesicle comprising a functional derivative or fragment thereof of a MHC Class I protein. Without more guidance and direction from the instant specification, it would require undue experimentation by one of ordinary skill in the art to make and use the recited vesicle comprising a functional derivative or fragment thereof, of a MHC Class I protein.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In view of the quantity of experimentation

necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

This rejection has been avoided in part by amendment of the claims and traversed in part as follows. Applicant has amended the claims to recite that the cell is a B lymphocyte and has deleted the phrase "or a functional derivative or fragment thereof" from the claims. The Examiner noted that the instant specification discloses in its examples, an antigen presenting vesicle derived from B cells.

The second rejection raised under this item is concerned with the Examiner's statement that it would require undue experimentation in view of Zitvogel et al to practice the claimed invention. Not only was Zitvogel published after the priority date of the subject application, but Zitvogel does not mention anywhere that MHC Class I does not work. So it is not seen why the person of ordinary skill in the art would have reason to doubt that the invention would work as claimed. It is well known that lymphocytes, such as a human B cell line used to generate vesicles in the present invention, generally express higher levels of MHC Class I proteins than any other cell in the body, which, in part, explains their presence on lymphocyte-derived vesicles. Thus, in view of the specification and the body of knowledge available in the art, the skilled artisan, rather than doubting the objective truth of the statements in the specification, would recognize that the disclosed methods for preparation of vesicles from antigen presenting cell would yield vesicles with MHC class I molecules on their surfaces. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

35 U.S.C. §112 First Paragraph Rejection, written description

Claims 13, 2, 3, 4 and 6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a written description of an antigen presenting vesicle comprising a membrane and any MHC Class I protein, or any functional derivative or fragment thereof, nor of an antigen presenting vesicle obtainable from any cell other than an antigen presenting cell.

The instant specification provides insufficient description of cells other than antigen presenting cells from which the recited vesicles would be obtainable. The instant specification discloses in its examples, an antigen presenting vesicle derived from B cells only, and Janeway et al (Immunobiology 3rd Edition) who teaches that antigens are presented by a limited number of cell types see page 7:15. Therefore, one of ordinary skill would not know if one was in possession of a cell type

from which the recited vesicle could be obainable without a further description of the cells in the instant specification.

The instant specification provides insufficient description of antigen presenting vesicles which comprise a functional derivative or fragment thereof of a MHC Class I protein because the instant specification neither defines nor describes a functional derivative or fragment thereof of a MHC Class I protein and the prior art does not teach such a vesicle. Therefore, one of ordinary skill would not know if one was in possession of the recited vesicle comprising a functional derivative or fragment thereof, of a MHC Class I protein without a further description of the vesicle in the instant specification.

Applicant is directed to the Revised Interim Guidelines for the Examinations of Patent Applications Under the 35 U.S.C. 112 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

This rejection is respectfully traversed because the subject matter of the claims appears in the claims originally filed in the PCT application from which the subject application entered national phase in the US and thus the Applicants were indeed in possession of the claimed invention at the time that the application was filed.

Original PCT Claim 1 broadly recited:

1. Antigen presenting vesicle free from its natural surroundings obtainable from antigen presenting cells.

Dependent claim 2 recited that the vesicle comprised inter alia at least a biologically active part of MHC Class I and Claim 6 recited inter alia that the vesicle could be derived from a B-lymphocyte.

In the preliminary amendment filed when the application entered national phase in the US, Claim 1 was cancelled and Claim 13 was added which included language from Claim 1 as filed and is also found on page 5, line 35 through page 6, line 6. The language of Claims 1 and 2 was combined in Claim 2. Claim 6 was amended to depend from Claim 13. That a component of a vesicle is a membrane is well-known to those of skill in the art as was discussed in the Response to Advisory Action, page 4, mailed July 17, 2001. The following is the text of the claims as submitted in the Preliminary Amendment.

13. An antigen presenting vesicle free from its natural surroundings obtainable from an antigen presenting cell, comprising:

a membrane and a major histocompatibility complex (MHC) protein or a functional derivative or fragment thereof. - - .

2. (Amended) The antigen presenting [Vesicle] vesicle according to claim [1] 13, wherein [comprising at least a biologically active part of an] said major histocompatibility [complex] complex protein is derived from MHC class I or class II [or a derivative thereof].

6. (Amended) The [Vesicle] antigen presenting vesicle according to [anyone of the aforegoing claims] claim 13, wherein said antigen presenting cell [which] is derived from a B-lymphocyte, a Langerhans cell, a macrophage or a dendritic cell.

Claim 13 as amended in the instant response combines the language of the above Claims 13 and 6 and additionally includes the language of Claim 3 from the PCT application as filed which recited that the vesicles additionally comprised at least partly processed antigens. This language also appears in the specification at page 6, lines 3-6. Claim 13 now reads as follows:

13. (Amended) An antigen presenting vesicle free from its natural surroundings, said vesicle comprising:

a membrane, [and] a major histocompatibility complex (MHC) class I protein [or a functional derivative thereof] and one or more at least partially processed antigens bound to said MHC class I protein, wherein said antigen presenting vesicle is obtainable from [an antigen presenting cell] a B lymphocyte.

Thus the patent specification adequately describes the claimed subject matter and the Examiner is respectfully requested to withdraw this rejection.

35 U.S.C. §112 Second Paragraph Rejection

Claims 2-4, 6 and 13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

A) Claim 2 is indefinite because the recited phrase "said major histocompatibility complex protein" lacks antecedent basis in claim 13. It is noted that claim 13 recites "a major histocompatibility complex (MHC) class I protein or a functional derivative or fragment thereof. Therefore, it is noted that Claim 13 does not encompass a major histocompatibility complex protein derived from MHC Class II.

B) Claim 6 is indefinite because the recited phrase "herein said antigen presenting cell" lacks antecedent basis in claim 13.

C) Claims 2-4, 6 and 13 are indefinite in the recitation of the phrase "or fragment thereof" in line 3 of claim 13, because it is not clear whether said phrase modifies the term "derivative" or the phrase "class I protein" or both.

[released by dendritic cells]. Indeed, in EBV-transformed B lymphocytes, multivesicular late endosomes do not express TfR").

Because the vesicles in the Harding and Zitvogel reference originate from different sources (macrophages versus DCs) an inherent present of MHC-II (based on disclosure in DCs), also in light of the above-cited difference, these references do not anticipate the claimed invention. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Amigorena

Amigorena et al (Nature (1994) 369: 113-120) describe a new populaton of Class II-enriched vesicles (abstract, second sentence) which they called Class II-containing vesicles (CIIV) (page 114, right column, second paragraph, first sentence). Because the vesicles in the Amigorena and Zitvogel references originate from differenct sources (B cells versus DCs), these references do not anticipate the claimed invention and the Examiner is respectfully requested to withdraw this rejection.

Formal Drawings.

Replacement formal drawings for Figures 1-4 are attached hereto which have been corrected in view of the Notice of Draftsperson's Review dated October 5, 1998 items 2, 10 and 12.

CONCLUSION

In view of the above amendment and remarks, it is submitted that this application is now ready for allowance. Early notice to that effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at: (831) 648-3090.

Respectfully submitted,

Date: August 7, 2002

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PATENT

ATTORNEY DOCKET NO. VEOC.001.01US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Johannes J. Geuze *et al.*

Serial No.: 09/011,167

Filed: October 5, 1998

Title: **CELL DERIVED ANTIGEN PRESENTING VESICLES**

Examiner: Amy M. DeCloux, Ph.D.

Art Unit: 1644

"MARKED UP" VERSION OF THE CLAIMS

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This "marked up" version of the claims accompany the attached Response to Office Action for the above identified patent application.

IN THE CLAIMS:

13. (Amended) An antigen presenting vesicle free from its natural surroundings, said vesicle comprising:

a membrane, [and] a major histocompatibility complex (MHC) Class I protein [or a functional derivative thereof] and one or more at least partially processed antigens bound to said MHC class I protein and wherein said antigen presenting vesicle is obtainable from [an antigen presenting cell] a B lymphocyte.

CERTIFICATE OF FIRST CLASS MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231:

August 7 2002
(Date)

K Patchen
(Signature)

Karen Patchen
(Printed Name)

14. (New) The antigen presenting vesicle according to Claim 13, wherein said vesicle is obtained by the step of recovering a 70,000 x g pellet obtained by differential centrifugation of membrane-containing fractions of cell culture media or lysates of B lymphocytes containing said MHC Class I protein.

15. (New) An antigen presenting vesicle free from its natural surroundings, said vesicle comprising:

a membrane, a major histocompatibility complex (MHC) Class I protein and one or more at least partially processed antigens bound to said MHC Class I protein, and wherein said antigen presenting vesicle is derived from culture media of B-lymphocytes containing said MHC Class I protein.

16. (New) An antigen presenting vesicle free from its natural surroundings, said vesicle comprising:

a membrane, a major histocompatibility complex (MHC) Class I protein and one or more at least partially processed antigens bound to said MHC Class I protein, wherein said antigen presenting vesicle is obtained by the step of recovering a 70,000 x g pellet obtained by differential centrifugation of membrane-containing fractions of cell culture media or lysates of B-lymphocytes containing said MHC Class I protein.

17. (New) An antigen presenting vesicle free from its natural surroundings, said vesicle comprising:

a membrane, a major histocompatibility complex (MHC) Class I and Class II proteins and one or more at least partially processed antigens bound to said MHC proteins, wherein said antigen presenting vesicle is obtained by the step of recovering a 70,000 x g pellet obtained by differential centrifugation of membrane-containing fractions of cell culture media or lysates of B-lymphocytes containing said MHC Class I and Class II proteins.

Respectfully submitted,

Date: August 7, 2002

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